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Review article

Autoimmunity, neuroinflammation, pathogen load: A decisive crosstalk in neuropsychiatric SLE

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ABSTRACT

Depicting the cellular and molecular bases of the continuous dialogue existing between the peripheral immune and the central nervous systems, as in neurolupus, is fundamental to improve, and better apprehend the role played by immune cells and mediators in the initiation and progression of neurological and psychiatric diseases, which nowadays remain a major public health issue. The relative frequency of neurological symptoms occurring in systemic autoimmunity is particularly worrying as, for example, two-thirds of patients with lupus will eventually experience the disabling effects of neuropsychiatric lupus. Neurolupus is a particularly severe form of lupus with wide-ranging symptoms, which contribute to increased mortality and morbidity in patients. In this context, infections, which suddenly trigger exacerbations of the otherwise mild lupus disease, may drive the progression of neuroinflammation and neurodegeneration *via* different mechanisms involving a network of effector molecules and cells. The complex interaction of neuroimmunology and neuroinfectiology represents a genuine challenge for basic scientists and clinicians to understand the mechanisms that are implicated, and identify possible biomarkers of severity that might predict the development of this devastating form of lupus. The ultimate goal is to design appropriate, personalised therapeutic strategies to improve the outcome of the disease.

Contents

Abbreviations: Abs, antibodies; AID, autoimmune disease; BBB, blood-brain barrier; CMA, chaperone-mediated autophagy; CNS, central nervous system; CSF, cerebrospinal fluid; DAMP, damage-associated molecular pattern; DCs, dendritic cells; ECs, endothelial cells; ICs, immune complexes; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NMDAR, *N*-methyl-D-aspartate receptor; NPSLE, neuropsychiatric systemic lupus erythematosus; NR2, *N*-methyl-$_D$-aspartate receptor subtype 2; NSPA, neuronal surface P antigen; O&NS, oxidative and nitrosative stress; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; TNF, tumour necrosis factor; UV, ultraviolet.

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1. Introduction

It has long been established that neuropsychiatric (NP) diseases can be elicited by infectious pathogens, diet, or environmental components [1]. Despite intensive investigation, however, the aetiology of most NP diseases as well as autoimmune diseases (AIDs) remains elusive. The interplay of hormonal, immunological, and environmental factors associated to a genetically-predisposed ground appears to be central but nowadays, it is not known how these intrinsic and extrinsic factors associate to trigger the disease, what are the host elements that are involved to orientate the form of the disease in a particular individual, and what regulates acute exacerbation and remission phases in certain AIDs. Autoimmunity may profoundly impact the continuous crosstalk held between the central nervous system (CNS) and the immune system contributing to the emergence of symptoms such as depression, mood and anxiety disorders, or psychosis [2–4]. Some of these symptoms have been reported to occur in neuropsychiatric systemic lupus erythematosus (NPSLE).

In this complex picture, infections have been described as decisive factors that not only trigger but also sustain and exacerbate AIDs. Epidemiological studies show that the occurrence of SLE differs according to countries, to areas of the same country and between social groups. These differences suggest that besides genetic susceptibility and intrinsic factors, environmental elements, notably the infectious environment and the level of hygiene in different world areas, are central in the development of this syndrome [5]. The composition of gut microbiota [6], which may change as a function of diet modification or following medication, can also modulate and aggravate the course of SLE.

After summarizing the current consensus views of NPSLE pathogenesis, this review will focus on the possible ways infectious agents may influence autoimmunity, the mechanisms of neuroinflammation and inflammation-induced behaviour, what they imply in terms of blood-brain barrier (BBB) permeability, brain cytokines and how, nowadays, we progress in our understanding of neurodegeneration in NPSLE. A better understanding this “ménage à trois” (brain, immune system and infectious agents) in a disease where there is still no specific treatment, is pivotal in our quest to design novel therapeutic options based on personalised approaches.

2. Neuropsychiatric systemic lupus erythematosus

2.1. Symptomatology

SLE is a prototypic relapsing-remitting AID identified by elevated titres of inflammatory mediators, hyper-activation of peripheral B and T lymphocytes, production of potentially pathogenic autoantibodies (autoAbs), clearance failure and tissue deposition of immune complexes (ICs). These events precede inflammatory conditions, which may cause end-organ damage [7]. SLE prevalence fluctuates from 40 to 100 cases per 100,000 individuals, and even 40 to 200 among blacks in the US [8,9]. The influence of hormones is central as 90% of patients are female and the vast majority of cases occur during childbearing age. Linkage between genetic and environmental factors (e.g. infections, pollutants, UV radiation, stress) might underpin disease bursts and justify the “waxing and waning” symptoms [10,11]. Although skin, arthritis and renal lesions are the most common manifestations, neurological and NP symptoms occur frequently [12]. When severe, they substantially contribute to the morbidity and mortality rates of patients [13].

NPSLE is a yet poorly understood disease that encompasses some twenty central and peripheral symptoms (Table 1). CNS symptoms largely predominate (93%) and may be diffuse or focal [14]. The majority of NP manifestations appears early in the course of SLE, most of them being not correlated with flare or severity of the disease. NPSLE is essentially clinically-defined by physical examination, brain imaging, and serological, psychiatric and neuropsychological tests. However, despite improved imaging, diagnosing NPSLE still remains a challenge [15–18]. The prevalence of NP events ranges from 14% to 75% [19,20], reflecting important differences in patient selection resulting from the absence of consensus for diagnosing NPSLE. The genetics of NPSLE has rarely been addressed. Of note, the gene *TREX1* involved in apoptosis, oxidative stress and several cerebral diseases has been linked to NPSLE [21]. Larger genome-wide association studies of lupus patients are therefore eagerly awaited.

2.2. Pathogenesis

The pathogenesis of NPSLE is particularly complex. The presence of a chronic inflammatory state is commonly reported but no single pathogenic dysfunction accounts for all NP symptoms, which result from several pathogenic pathways including vascular and neuroinflammatory circuits (Fig. 1) [14,22,23].

Much data demonstrate that some NP symptoms are caused by antiphospholipid Abs, which bind to clotting factors and endothelial cells (ECs), inducing a pro-coagulant state. This mostly results in focal manifestations that can be associated with structural brain abnormalities at autopsy [24]. Both in murine models of lupus [25–28] and in patients [29,30], diffuse manifestations were found to result rather from inflammatory processes and toxicity mediated by Abs binding neuronal cell surface receptors, such as neuronal surface P antigen (NSPA) and *N*-methyl-D-aspartate receptor